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Model 7250 Jewel® AF
AF Only Clinical Evaluation

Introduction

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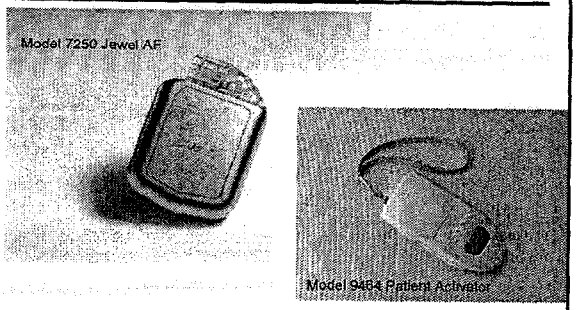
Circulatory System Devices Panel Presentation

Dec 5, 2000

System Description



System Description

Model 7250 Jewel ® AF

- Studied /FDA Approved in VT/AT population June 2000
- Comparable to other Medtronic ventricular ICDs
- Includes features intended for treatment and prevention of atrial tachyarrhythmias
  - Atrial Tachyarrhythmia Termination
    - Antitachycardia Pacing (ATP)
    - High Frequency Burst (HFB)
    - Atrial Shock – automatic, or patient activated
  - Atrial Tachyarrhythmia Prevention
    - Atrial Rate Stabilization (ARS)
    - Switch Back Delay ("Cool Down")

System Description

- Model 9464 Patient Activator
  - Battery-powered, radio-frequency hand-held device
  - Used to self-activate shocks for atrial tachyarrhythmias
- Lead Model 6937A
  - 9 French, unipolar high voltage lead designed for placement in the CS or SVC
  - Similar to 6937 lead with slight differences

Model 7250 Jewel® AF Proposed Indications For Use

The Jewel AF system is intended to provide pacing, cardioversion, and defibrillation for treatment of patients with:

- Symptomatic, drug refractory atrial tachyarrhythmias and/or
- Life threatening ventricular tachyarrhythmias

Role of Device-Based Therapy For Atrial Tachyarrhythmias

- Part of an overall treatment strategy
- Symptomatic and drug refractory patients
- Estimated at 5% of total AF population
- For patients who need more control of their therapy
- For patients with frequent hospital visits for cardioversions

Presenters

- Michael Gold, MD, PhD — Study Results
- David Schwartzman, MD — Case Presentations
- David Newman, MD — Quality of Life

- Medtronic, Inc — Study Questions

Dennis Connolly, MD
Scott Brown, PhD
Reece Holbrook, BSEE

Linda Johnson, PhD
Roy Martin, DVM
Rahul Mehra, PhD
Nirav Sheth, PhD

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Model 7250 Jewel® AF AF-Only Study

Study Results

Michael Gold, MD, PhD

Circulatory System Devices Panel
Dec. 5, 2000

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Study Purpose

- Demonstrate the safety and efficacy of the Model 7250 Jewel AF® in patients suffering from symptomatic, drug refractory atrial tachyarrhythmias *without* ventricular ICD indications.

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Study Design

- Multi-center IDE Study
- Prospective follow up study for safety and efficacy of treatment therapies
- Randomized, crossover study for evaluation of prevention therapies
  - 3 months ON, 3 months OFF

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Study Inclusion Criteria

- Patient must have experienced 2 atrial fibrillation/flutter episodes within last 3 months
  - 1 episode with ECG documentation
- Episodes must be symptomatic
- Patient must be drug refractory or intolerant
  - patient failed ≥ 1 antiarrhythmic drug
- Patient must be in sinus rhythm at time of implant
  - if post-cardioversion SR ≥ 1 hour

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Study Exclusion Criteria

- Chronic AF (< 1hr SR post cardioversion)
- History of uncontrolled angina
- History of sustained VT/VF (>30 seconds of hemodynamically unstable VT/VF)
- NYHA Class IV heart failure
- Cardiac surgery within 1 month
- Atrial thrombus detected within last 6 months prior to implant
- CVA within 1 year
- Unwilling to give informed consent
- Mechanical tricuspid heart valve
- Life expectancy < 1 year

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Study Experience

- 144 implanted / 146 enrolled
  - From 11/21/1997 – 11/12/1999
  - United States (107), Europe(33), Canada (6)
- Follow-up
  - Database cutoff: May 31, 2000
  - Mean (SD): 12.7 (±6.1) months
  - Cumulative patient months: 1835
  - Range: 0.1 – 25.9 months

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Patient Characteristics

Male	71%
Mean Age	62 ± 12 yrs
CAD	32%
MI	19%
CHF	29%
Mean EF	51 ± 18 %
% EF ≤ 40%	31%
LA Size	46 ± 8 mm

- **AF Type**
  - Paroxysmal AF 35%
  - Incessant AF* 65%
- **Primary Indication**
  - AF 74%
  - AF/AFlutter 23%
  - Aflutter 3%

*Incessant AF (aka: Persistent AF) is defined as AF that does not spontaneously convert to SR, but can be cardioverted.

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Primary Objectives

- Safety
  - Estimate the relative risk (RR) of system/procedure-related complications for the Model 7250 vs the Model 7219D
  - The 95% upper confidence bound will be < 3.0
- Efficacy
  - Estimate the efficacy of atrial tachyarrhythmia termination therapies of the Model 7250
  - The 95% lower confidence bound will be > 75%

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Comparison to Historical Control (Model 7219D ICD) - Analysis Methods

- **Comparison to 7219D**
  - **primary safety endpoint: complication-free survival**
  - **Secondary onjective: survival from all-cause mortality**
- **Adjusted for differences in baseline patient characteristics in the two populations**
  - **Multi-variate Cox Proportional Hazzards Regression Model**

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Comparison to Historical Control (Model 7219D ICD) Analysis Method

Method:

Step 1. Compare two populations with univariate analyses (p-value 0.10) to find significant factors

Step 2. Determine which factors were predictive of the outcome variable with univariate analyses (p-value 0.10 or RR of at least 100 ± 20%) to find significant predictors

Step 3. Variables identified in Steps 1& 2 were put into a "best fit" model using a step-wise approach (p-value 0.05 or RR of at least 100 ± 20%)

- Variables in the final model for complication-free survival were:
  - region (US, non-US), gender, CAD, hypertension, cardiomyopathy, NYHA Class, CABG, SMVT
- Variables in the final model for survival from all-cause mortality were:
  - gender, CAD, MI, hypertension, cardiomyopathy, CHF, NYHA Class, CABG, valve surgery, AFib, AFlutter, SMVT

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Safety Primary Endpoint Results

- Relative Risk (RR) of system/procedure related complications for the Model 7250 vs the Model 7219D
  - 1.31 (95% LCB 0.76, 95% UCB: 2.25)
  - Safety Objective Met: 95% UCB 2.25 < 3.0

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System/Procedure Related Complications

Adverse Event	Number of Events	Number of Patients (%)
Lead Dislodgements	11	10(6.8%)
Atrial Fibrillation	3	3(2.1%)
Hematoma	2	2(1.4%)
Infection	2	2(1.4%)
Allergic Reaction	1	1(0.7%)
Anxiety	1	1(0.7%)
Patient Unable To Tolerate Therapy	1	1(0.7%)
Inappropriate Detection	1	1(0.7%)
Lead Failure	1	1(0.7%)
Pacemaker Syndrome	1	1(0.7%)
Skin Irritation	1	1(0.7%)
Undersensing	1	1(0.7%)
Total	26	23

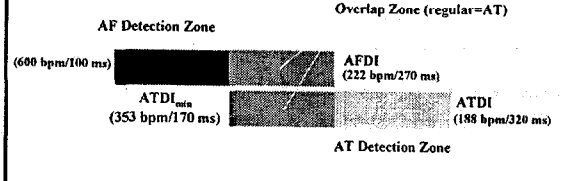
Complication-free Survival

- **System/procedure related complication-free survival @ 6-months**

7250 AF Only Number at risk: 108	86.6% (95%CI: 79.8, 91.3)
7219D Number at risk: 173	91.6% (95% CI: 88.8, 93.8)

AT/AF Rhythm Classification

Programmable Detection Zones



Efficacy: Success/Failure of Termination Therapy

- Device Classification of Termination
  - Success is defined as 5 consecutive sinus beats within 3 minutes of therapy delivery without redetection.
- Reported Therapy Efficacy
  - **Crude proportion** is the number of episodes terminated by a specific therapy divided by the number of episodes treated with that type of therapy.
    - *What is the probability that a randomly selected episode will be terminated?*
  - **Generalized Estimating Equation Adjusted Proportion (GEE)** is the average of the average efficacy for each patient; corrects for multiple episodes in individual patients.
    - *What is the probability that a randomly selected episode from a randomly selected patients will be terminated?*

Efficacy Primary Endpoint Results

- **91% efficacy for atrial tachyarrhythmia termination therapies**
  - Evaluates all episodes with at least 1 shock in the therapy sequence
  - 1092 of 1200 AT/AF episodes in 107 patients terminated
  - Crude Efficacy Proportion: 91.0%
  - GEE Efficacy Proportion: 85.9% (95% LCB:81.7%, 95% UCB 89.2%)
- **Efficacy Objective Met: LCB 81.7% > 75%**

Secondary Objectives & Additional Analyses

Efficacy – Number of Shocks per Episode

- Number of Atrial Shocks Per Episode
  - 1200 AT/AF episodes in 107 patients
  - Mean # shocks per episode = 1.19

1 shock	86.1%
2 shocks	10.1%
3 shocks	2.1%
4 shocks	0.7%
5 shocks	0.1%
6 shocks	0.2%
10 shocks	0.1%

Efficacy Of Atrial Shock Therapy For AF

- 92.4% Atrial Shock Therapy Efficacy for AF episodes only
  - 1868 total AF episodes in 102 patients
  - 723 in 85 patients treated with shock
  - 668 successfully terminated
  - Crude efficacy proportion: 92.4%
  - GEE proportion: 88.4% (95% CI: 83.3%, 92.1%)

Efficacy – Patient Activated Shocks

- **92.8% Patient Activated Shock Therapy Efficacy for AT/AF**
  - Evaluates all episodes with at least 1 patient activated shock in the therapy sequence
  - 519 of 559 AT/AF episodes in 67 patients terminated
  - Crude Efficacy Proportion: 92.8%
  - GEE Efficacy Proportion: 89.1% (95% CI: 83.8%, 92.8%)

Pacing Efficacy

	Episodes (patients)	Efficacy Crude Proportion	Efficacy GEE
ATP & HFB for AT/AF	1560/4466 (109 patients)	34.9%	28%
ATP for AT	1049/2720 (89 patients)	38.6%	32.1%
HFB for AT/AF	449/2964 (99 patients)	15.1%	12.2%
ATP & HFB for AT	1212/2896 (92 patients)	41.9%	35.5%
HFB for AT	163/1394 (74 patients)	11.7%	10.6%
HFB for AF	286/1570 (86 patients)	18.2%	14.1%

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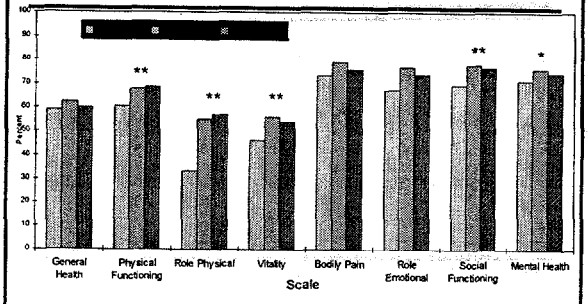
Impact On Quality Of Life
SF-36 Scale Scores Over Time (N=84)



* Significant improvement from baseline to 3 months
** Significant improvement from baseline to both 3 & 6 months

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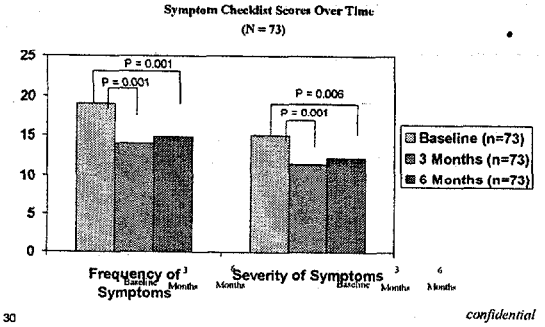
Impact On Quality of Life
Symptom Burden Over Time



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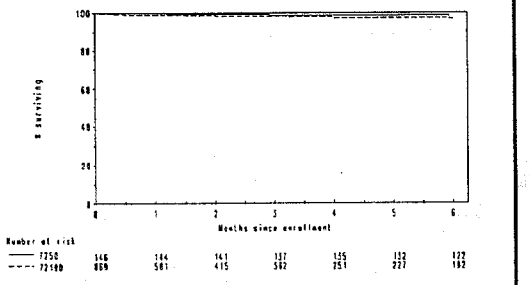
Mortality

- Estimate the relative risk (RR) of death as compared to the 7219D study
  - Adjusted RR for the 7250 is 0.51
  - 0.51(95% LCB 0.12, 95%UCB 2.17)

Comparison of 7250 AF-Only & 7219D Survival Curves



Survival From All-Cause Mortality

- **Comparison of 6-month Kaplan-Meier all-cause survival rates**

7250 AF-Only	98.6%
Number at risk: 122	(95% CI: 94.5, 99.6)
7219D	96.4%
Number at risk: 192	(95% CI: 93.7, 98.0)

Positive Predictive Value of Atrial Detection

- 98.8% PPV for detection of atrial tachyarrhythmias
  - 4913 total spontaneous atrial episodes detected by the device
  - 4859 atrial episodes appropriately detected (per investigator classification)
  - Crude Proportion PPV: 98.8%
  - GEE Proportion: 98.6% (95%CI: 96.0%, 99.5%)

Effects of Prevention Therapies

- Evaluation of Atrial Rate Stabilization and Switch Back Delay Pacing Features
  - 75 patients completed the randomized 3 months ON vs OFF protocol
    - n = 38 ON-OFF
    - n = 37 OFF-ON
  - No significant difference in frequency of episodes (p=0.72)

Atrial DFTs

- Mean Atrial DFTs
  - two-tiered step-up protocol
    - At implant (n = 86)
      - 6.8 joules ± 4.8 joules

Atrial Shock Induced VT/VF

- No incidence of atrial shock induced VT/VF
  - 0% (95% CI: 0.0%, 0.3%)

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Incidence of Spontaneous VT/VF

- 11 (7.6%) patients had 67 spontaneous, appropriately detected ventricular episodes
  - 16 episodes of spontaneous "VF" (CL < 300 ms)
  - 51 episodes of VT (CL 310-360 ms)
- VT/VF therapies
  - 57 episodes in 6 patients successfully treated with ATP or shock
  - 10 episodes in 5 patients terminated spontaneously after 9-220 sec.

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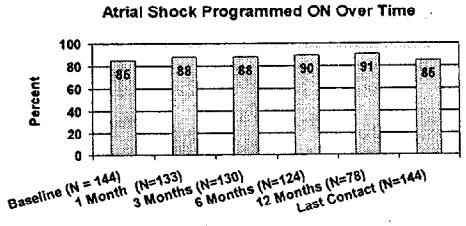
Atrial Shock Programming

Physicians consistently programmed shocks ON.



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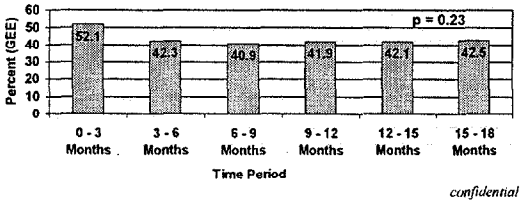
Use of 9464 Patient Activator

- 67 patients used the 9464 Patient Activator to treat 559 episodes
- 90.5% of episodes treated with 1 shock
- 92.8% (519) of episodes were successfully terminated (89.1% GEE)
- Over 70% of patients had patient activated shock programmed "ON" at last contact

Use of 9464 Patient Activator

Patients consistently used the Patient Activator over time; in total, treating 46.6% (GEE) of all long episodes.

Use of Patient Activated Shocks For Episodes > 30 Minutes



6937A Lead Patient Experience

- 55% (79/144) AF Only and 7% (35/530) VT/AT patients implanted with the 6937A lead
- 111 of 114 implanted in the CS
- Mean Follow-up 12.8 months ± 6.2
- 6937A Lead related AEs: 3 atrial lead dislodgements; 1 subclavian vein thrombosis
- 3 month complication-free survival
  - 97.3% (95% LCB 93.2%, 95% UCB xx.x%)
- Atrial DFTs (n = 63)
  - Mean (SD) 6.2 joules ± 4.6

Conclusion - Risk vs. Benefit

Risks – Similar to ventricular defibrillators

Benefits – New tool for AF treatment strategy

- Highly effective Atrial Defibrillator
- Maintenance of Sinus Rhythm
- Pacing Therapies offer incremental efficacy with low risk
- Patient Control of therapy
- Enhanced Monitoring for chronic, non-static disease
- Improved Quality of Life
- Physician and Patient Acceptance
- Ventricular Arrhythmia Protection

Conclusion

The 7250 Jewel AF Only Clinical Evaluation shows the Jewel AF Model 7250 System is *safe* and *effective* in patients with Atrial Tachyarrhythmias.